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EXAMINER

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/544,910	Applicant(s) HUANG ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-8 and 11-35 is/are pending in the application.
- 4a) Of the above claim(s) 12-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-8 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1,4-8 and 11-35 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Continued Prosecution Application

1. The request filed on January 9, 2002 in Paper No. 17 for a Continued Prosecution Application (CPA) under 37 CFR § 1.53(d) based on parent Application No. 09/544,910 is acceptable and a CPA has been established. An action on the CPA follows.
2. The amendment filed on November 8, 2001 in Paper No. 13 is acknowledged and has been entered. Claims 2, 3, 9, and 10 have been canceled. Claims 1 and 5 have been amended.
3. Claims 11, 4-8, and 11-35 are pending in the application. Claims 12-35 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a non-elected invention.
4. Claims 11, 4-8, and 11 are currently under prosecution.

Specification

5. The disclosure is objected to because of the following informalities:

The upper margins are not large enough to accommodate the holes that are necessarily punched in order to attach the papers to the file wrapper without removing a portion of the text. A substitute specification with larger margins to accommodate the holes is required.

Claim Rejections Withdrawn

6. In the Office Action mailed January 29, 2001 (Paper No. 9), claims 1-11 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to recite a positive process step that clearly relates back to the preamble of the claims.

In the amendment filed November 8, 2001 (Paper No. 13), Applicants amended claims 1 and 5 to recite a positive process step that clearly relates back to the preamble of the claim. While the amendment has not altered the scope of the claims, the present claims more particularly point out and distinctly claim the subject matter that Applicants regard as their invention, since it would now be evident to one of ordinary skill in the art that each and every step that Applicants consider essential in practicing the invention to achieve the objective of the claim, as set forth in the preamble, is recited in the body of the claim. Thus, this ground of the rejection has been rendered moot by the amendment, and accordingly the rejection of claims 1, 4-8, and 11 under 35 USC § 112, second paragraph is withdrawn.

Claim Rejections Maintained and Response to Applicants' Remarks

Claim Rejections – 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office Actions mailed January 29, 2001 (Paper No. 9) and August 9, 2001 (Paper No. 12).

The subject matter of the claimed invention is not described in the specification in such a way as to reasonably convey to the skilled artisan that Applicant had possession of the invention at the time the application was filed. The specification fails to set forth a disclosure identifying a specific agent that can be used to practice the invention successfully. The specification fails to set forth exemplification, prophetic or otherwise that might demonstrate that the invention can be used successfully to reduce the

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plasma level of VLDL and triglycerides in a host. The specification fails to set forth exemplification, prophetic or otherwise that might demonstrate that the invention can be used efficaciously to treat a host suffering from a disease condition associated with elevated levels of VLDL and/or triglycerides. As such there is no factual evidence set forth in the specification that would reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

Applicants have traversed the rejection in Paper No. 13, stating, "one of ordinary skill in the art would recognize that the Applicants invented what is claimed" (page 4, paragraph 2). Applicants assert, "the specification provides ample guidance such that one skilled in the art could use the specification, coupled with what is known in the art, to practice the claimed method", claiming that the disclosure details several methods for decreasing the expression of apoE (page 5, paragraph 2). Applicants further assert that the applicability of antisense technology to reduce apoE expression has been established, citing Charpentier, et al (*Biochemistry* **39**: 16084-16091, 2000) in support of this assertion. Applicants state that animal models are provided and methods for screening candidate agents using these animal models to identify an effective agent that could be used to practice the claimed methods are disclosed in the specification. Applicants argue, "[a]ll that is necessary to fulfill the written description requirement is that one of skill in the art recognize that the Applicants invented what is claimed", citing MPEP § 2163.02 in support of this argument.

In reply to Applicants' arguments, while one might recognize that Applicants contemplated the invention, in the absence of factual evidence, the skilled artisan would not reasonably conclude that Applicants had possession of the claimed invention at the time the application was filed. Evidence of contemplation is not evidence of a reduction to practice, or evidence that Applicants had successfully practiced at least a substantial number of the methods encompassed by the claims. Applicants' statement, "the specification provides ample guidance such that one skilled in the art could use the specification, coupled with what is known in the art, to practice the claimed method" does not provide evidence that Applicants had possession of the claimed invention at the time the application was filed; actually Applicants' statement seems more properly

directed as a rebuttal of the assertion that the disclosure is too inadequate to meet the enablement requirement of 35 USC § 112, first paragraph, rather than of the present grounds of rejection. The disclosure to which Applicants have referred in their remarks sets forth conventional knowledge in the art, which fails to reasonably convey that Applicants had possession of the claimed invention at the time the application was filed. Notably, although the claims are not limited to a method comprising administering an antisense oligonucleotide to a host, the disclosure to which Applicants have referred is so limited. Nevertheless, the description of antisense technology is so general that it would not reasonably convey to the skilled artisan that Applicants had possession of a method for reducing the plasma level of VLDL in a host by administering to the host an antisense oligonucleotide molecule. In particular, it is noted that the specification fails to describe the antisense oligonucleotides that can be used to successfully practice the method, or to describe regions of the polynucleotide sequence of the gene that can be effectively targeted by an antisense oligonucleotide so as to diminish expression of the gene. Furthermore, the disclosure fails to describe the level of inhibition of expression of the gene that might be achieved in practicing the claimed method, or which level of inhibition must be attained to effectively reduce the plasma level of VLDL in the host.

Applicants cite Charpentier, et al, suggesting that their report provides evidence that the invention can be practiced successfully. However, supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a). Nevertheless, again, Applicants' arguments are more germane to the enablement inquiry under 35 USC § 112, first paragraph, rather than the written description inquiry. Certainly, the teachings of Charpentier, et al would not suggest that Applicants had possession of the claimed invention at the time the application was filed.

In reply to Applicants' statement that the disclosure provides animal models and methods for screening candidate agents using these animal models to identify an effective agent that could be used to inhibit the expression of the gene encoding apoE, perhaps Applicants should consider whether the disclosure better supports claims

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drawn to such inventions, rather than to the methods presently claimed in this application.

Finally, as Applicants have noted, according to MPEP § 2163.02, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. However, the courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Accordingly, so that one of ordinary skill in the art given benefit of the disclosure, would recognize that Applicants invented that which is claimed in the application, the disclosure must describe the subject matter encompassed by the claims in sufficient detail to reasonably convey to the skilled artisan that the Applicants had possession of that subject matter at the time the application was filed. Therefore, contrary to Applicants’ arguments, to meet the written description requirement, the disclosure must do more than merely describe a means for making and using the invention. To meet the written description requirement, the disclosure must include a description of at least a substantial, or at least a representative number of embodiments of the methods encompassed by the claims, and of sufficient detail to satisfy a factual inquiry to determine whether the skilled artisan would have reasonable cause given only benefit of Applicants original disclosure, to accept the assertion set forth in the claims that Applicants had possession of the claimed invention as of the filing date sought.

The present disclosure does not include a description of at least a substantial number of embodiments of the methods encompassed by the claims, and does not include a description of at least a representative number of embodiments of the methods encompassed by the claims, and the descriptions of the embodiments that are included are not of sufficient detail to satisfy the factual inquiry, as the skilled artisan given only the benefit of the disclosure, would not reasonably conclude that Applicants

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had possession of the claimed invention at the time the application was filed. Therefore, although Applicants' arguments have been carefully considered, the disclosure is considered insufficient to meet the written description requirement of 35 USC § 112, first paragraph. Accordingly, the rejection of claims 1, 4-8, and 11 under 35 USC § 112, first paragraph is maintained.

9. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous Office Actions mailed January 29, 2001 (Paper No. 9) and August 9, 2001 (Paper No. 12).

The teachings of the specification cannot be extrapolated to the enablement of the invention because the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims. Moreover, in the absence of sufficient guidance, direction, and exemplification, the skilled artisan could not practice the claimed invention with a reasonable expectation of success without need to first perform undue experimentation. The recitation of a catalog of putatively effective generic agents is insufficient to enable the skilled artisan to practice the invention with a reasonable expectation of success without undue experimentation, because the skilled artisan cannot predict which, if any of the agents disclosed can be used effectively.

Applicants have traversed these grounds of rejection, contending to the contrary, "the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation" (page 6, paragraph 2). Applicants point out, "the test of enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine" (page 6, paragraph 3). Applicants assert, "[o]nce a skilled artisan has identified a gene target, reducing its expression is well within that artisan's skill with no more than routine experimentation" (page 6, paragraph 3). Then, Applicants state,

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"the claims only require the Applicants to demonstrate that apoE affects VLDL production and also plasma level of VLDL" (page 8, paragraph 1).

In reply to Applicants' arguments, the claims are not limited to a method comprising administering an antisense oligonucleotide to a host to inhibit the expression of the gene encoding apoE and thereby reduce the plasma level of VLDL in the host. Nevertheless, contrary to Applicants' assertion, the art of antisense oligonucleotide-mediated therapy is not conventional, nor are the studies or methodology routine. In the abstract, Sohail, et al (*Current Opinions in Molecular Therapy* 2: 264-271, 2000) teach,

Despite the simplicity of the concept, almost every step in an antisense experiment poses difficulties. Finding a site that is accessible to intermolecular hybridization with complementary nucleic acids is a major problem and determines the success or failure of an antisense experiment. A major determinant of accessibility appears to be the intramolecular folding in mRNAs that renders much of the molecule inaccessible. However, owing to our poor understanding of RNA folding and the mechanisms of heteroduplex formation, theoretical methods have limited use in finding accessible sites. Such methods are unable to address two major considerations when describing an antisense reagent, i.e., which is the most accessible sequence in the target and what length of the reagent works best in terms of activity and specificity. Empirical approaches appear more successful.

Also with regard to the evident lack of conventionality in the art, Pierce, et al (*Nucleic Acids Research* 26: 5093-5101, 1998) explain,

A key parameter in the success or failure of an antisense therapy is the identification of a suitable target site on the chosen mRNA. Ultimately, the accessibility of the target to the antisense agent determines target suitability. Since accessibility is a function of so many complex factors, it is currently beyond our ability to predict.

Thus, contrary to Applicants' assertion, once a skilled artisan has identified a gene target, reducing its expression is not routine.

Furthermore, despite the voluminous number of studies that have been performed, the many limitations of antisense therapy have yet to have been overcome. In particular, the pre-clinical application of antisense therapies have met with little success due to the inherent instability of the antisense molecules *in vivo*, which to some extent results from susceptibility to nucleases, due to the inability to effectively deliver

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the antisense reagents to the targeted tissues, which has wrought undesirable, adverse non-specific toxicity, and due to non-specific hybridization, which also may have undesirable effects. For example, Lesoon-Wood, et al (*Cancer Letters* **147**: 163-173, 1999) discovered that control antisense molecules, which were expected not to have an effect, caused a considerable level of non-specific inhibition of expression. Moreover, Lesoon-Wood, et al found that the control antisense molecule enhanced the neoplastic transformation of cells treated with the molecule.

In more particular regard to the methods presently claimed in this application, although Applicants assert "the claims only require the Applicants to demonstrate that apoE affects VLDL production and also plasma level of VLDL" and presumably, the claimed invention is thereby enabled, there is evidence that reducing the level of apoE expression in a host may not be an effective means for treating a patient diagnosed with a disease associated with dyslipidemia. Ishigami, et al (*Journal of Biological Chemistry* **273**: 20156-20161, 1998) teach, "[t]aken together, these results suggest that apoE has cytostatic functions in the vessel wall and may **protect** against vascular disease through inhibition of cell signaling events associated with growth factor-induced smooth muscle cell migration and proliferation" (emphasis added) (abstract). Accordingly, practicing the claimed method may paradoxically promote the formation of arteriosclerosis, rather than reduce its incidence, or measure. Also, as noted in Paper No. 12, Huang, et al (cited in Paper No. 9) teaches that too little apoE impairs clearance of triglyceride-rich lipoproteins and their remnants from plasma, indicating that apoE is necessary for normal metabolism. Thus, the teachings of Huang, et al, like those of Ishigami, et al, suggest that inhibiting the expression of apoE may be more detrimental to the patient than beneficial. Therefore, in the absence of working exemplification, the skilled artisan could not practice the claimed invention without first determining whether or not the agent can be used successfully, and this determination would require undue experimentation. In particular, because of the known limitations to antisense therapy, the skilled artisan would not accept the assertion that an antisense oligonucleotide that inhibits the expression of apoE can be used efficaciously to treat patients diagnosed with hyperlipidemia.

Finally, in further reply to Applicants' arguments, it is noted that the courts have determined that antisense technology is highly unpredictable. See Enzo Biochem Inc. v. Calgene Inc., 52 USPQ2d 1129 (CAFC, 1999). Although the court acknowledged:

In view of the rapid advances in science, we recognize that what may be unpredictable at one point in time may become predictable at a later time. See *Vaeck*, 947 F.2d at 496, 20 USPQ2d at 1445 (" [W]e do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification.").

(*Id.* at 1143), as evidenced by the teachings of Sohail, et al, Pierce, et al, and Lesson-Wood, et al, in addition to those of Roush and James (cited in the Paper No. 9), the time that antisense technology has advanced to the point of predictability has not yet arrived.

As stated in the previous Office Actions, Applicants disclosure is viewed merely as an invitation to one skilled in the art to develop a method that might be used to effectively to reduce the expression of apoE to an extent sufficient to effectively reduce the level of VLDL in the plasma. As the court stated in:

As we stated in *Genentech*:

Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

See *Genentech*, 108 F.3d at 1366, 42 USPQ2d at 1005. We thus conclude that the district court did not clearly err in finding that the specifications provided little guidance or direction as to the practice of antisense in cells other than *E. coli*, and that such minimal disclosure as there was constituted no more than a plan or invitation to practice antisense in those cells.

Id. at 1138. Here, however, Applicants have provided comparably little disclosure, failing to disclose any guidance, direction, or working examples.

Thus, Applicants' arguments have been carefully considered but in view of the preponderance of evidence, have not been found persuasive. Accordingly, the rejection of claims 1, 4-8, and 11 under 35 USC § 112, first paragraph is maintained.

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Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ditschuneit, et al, as evidenced by Pedreno, et al and Durrington, et al for the reasons set forth in the previous Office Actions mailed January 29, 2001 (Paper No. 9) and August 9, 2001 (Paper No. 12).

In summary, Ditschuneit, et al teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Ditschuneit, et al administer to the patients an effective amount of gemfibrozil to reduce the concentrations of both VLDL and triglycerides in the patient's serum. As evidenced, by the teachings of Pedreno, et al, gemfibrozil causes a reduction in the level of plasma active apoE. Therefore, the method of Ditschuneit, et al causes a reduction in plasma active apoE. Thus, all the limitations of the claims are anticipated by the teachings of Ditschuneit, et al.

Applicants have traversed the grounds of this rejection, arguing the teachings of Ditschuneit, et al does not anticipate the presently claimed invention, since "the mechanism of action of gemfibrozil is through increasing LDL receptor expression, for which apoE is a ligand" (page 9, paragraph 1). Moreover, Applicants assert that the mechanism by which gemfibrozil mediates a reduction in the level of plasma VLDL in a patient is not the same as the mechanism of the agent administered to the host of the present claims.

In reply, as stated in the Office Action mailed December 11, 2001 (Paper No. 15), it is clearly unreasonable to assert that the mechanism by which an undisclosed agent reduces the expression of apoE, i.e., reduces the amount of active apoE in the plasma of the host, and the mechanism by which the agents of the prior art do so are different.

Although Applicants insist "the mechanism of action of gemfibrozil is through increasing LDL receptor expression, for which apoE is a ligand", Applicants have provided no factual evidence to support their assertion.

Furthermore, it is again noted that the claims are not limited to a method in which the level of transcription of the gene encoding apoE is reduced, or in which the level of translation of mRNA encoding apoE is reduced. For that matter, the claims are not limited to the use of an antisense oligonucleotide. The claims merely require that upon administration of an effective amount, the undisclosed agent reduce the expression of apoE; the mechanism by which the agent is required to reduce the expression of apoE is not recited in the claims. As evidenced by the teachings of Pedreno, et al, the agent of the prior art, namely gemfibrozil reduces the level of apoE in the plasma of patients to whom the agent is administered, so unless the agent increases the rate of clearance of apoE from the treated patients' plasma, it is reasonable to expect that gemfibrozil affects the expression of apoE. Again, it is not necessary that gemfibrozil directly affect the level of expression of apoE in the patient by a direct mechanism, as the claims only require the expression of apoE to be reduced by the agent.

Accordingly, the agent of the prior art is deemed that same as the agent of the present claims, absent a showing of any differences. The Office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the product referred to in the claims. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed method or the products encompassed by the claims are functionally different than those taught by the prior art and to establish patentable differences.

Furthermore, as noted in the previous Office Actions, the mechanism or mechanisms by which gemfibrozil affects the level of apoE are not fully understood. However, Clavey, et al (*Cellular Physiology and Biochemistry* 9: 139-149, 1999) have reported that fibrates, such as gemfibrozil, repress apolipoprotein CIII gene expression, an effect that partially explains the triglyceride-lowering activity of these drugs.

Therefore, contrary to Applicants' insistence, the mechanism of fibrates, such as gemfibrozil, is not limited to increasing LDL receptor expression. Furthermore, if the level of apoE is decreased in the serum of patients treated with gemfibrozil, it seems probable that the reduction in the level of apoE might be mediated by a reduction in its expression. In turn, a reduction in apoE expression might be mediated by an inhibition of transcription or translation, or by a post-translational mechanism; and again, the claims are not limiting.

Applicants' arguments have been carefully considered but not found persuasive, since Applicants have provided no factual evidence that the agent of the prior art and the agent of the present claims are different.

12. Claims 1, 3-8, 10, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshino, et al for the reasons set forth in the previous Office Actions mailed January 29, 2001 (Paper No. 9) and August 9, 2001 (Paper No. 12).

In summary of those reasons, Yoshino, et al teach a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Yoshino, et al administer to the patients an effective amount of pravastatin to reduce the concentrations of apoE, VLDL, and triglycerides in the patient's plasma.

Applicants have traversed the rejection of the claims under 35 USC § 102(b) arguing, "there is no evidence that pravastatin acts to decrease plasma VLDL by reducing expression of apoE, while there is evidence that it acts through a different mechanism in that is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase" (page 9, paragraph 4). Applicants contend that the teachings of Yoshino, et al cannot anticipate the claimed invention, because "the decrease in apoE [resulting from administering pravastatin to the patient] is not the result of decreased expression as the claims require" (page 9, paragraph 4).

In reply to Applicants' arguments, it is noted that Applicants have provided no evidence that pravastatin does not decrease the plasma VLDL by reducing expression of apoE. Although pravastatin is known to be an inhibitor of HMG-CoA reductase,

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Applicants have not provided any evidence that pravastatin does not affect the level of plasma VLDL by some other mechanism, such as directly affecting the level of expression of apoE. For that matter, Applicants have provided no evidence that as an inhibitor of HMG-CoA reductase, pravastatin reduces the level of apoE expression in patients treated with an effective amount of the agent.

Nevertheless, Wyne, et al (*Journal of Biological Chemistry* **264**: 16530-16536, 1989) teach that mevinolin, an inhibitor of HMG-CoA reductase, attenuates stimulation of transcription of the gene encoding apoE in rat granulosa cells upon exposure to cholera toxin or 12-O-tetradecanoylphorbol-13-acetate (TPA) in a dose-responsive manner (abstract). Thus, the teachings of Wyne, et al suggest that pravastatin mediates a reduction in apoE by affecting the level at which the gene encoding apoE is expressed.

Therefore, the agent of the prior art, namely pravastatin is deemed the same as the agent of the claims, absent a showing of any differences. Again, the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the product referred to in the claims. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed method or the products encompassed by the claims are functionally different than those taught by the prior art and to establish patentable differences.

13. Claims 1, 3-8, 10, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Connor, et al for the reasons set forth in the previous Office Actions mailed January 29, 2001 (Paper No. 9) and August 9, 2001 (Paper No. 12).

In summary of those reasons, Connor, et al teach a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Connor, et al administer to the patients an effective amount of dietary n-3 fatty acids to reduce the concentrations of apoE, VLDL, and triglycerides

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in the patient's plasma. Thus, all the limitations of the claims are anticipated by the teachings of Connor, et al.

Applicants traverse the rejection under 35 USC § 102(b) arguing, "[n]othing in the cited references teaches that apoE is a target for reducing the plasma level of VLDL or that reduction of apoE expression will cause a reduction in VLDL production and thereby also reduce plasma VLDL" (page 10, paragraph 3). Additionally, Applicants assert that there is evidence that n-3 fatty acids act through mechanism different from that of the undisclosed agent to which the claims are drawn.

In reply to Applicants' arguments, it is again noted that Applicants have not substantiated their assertions by the provision of factual evidence. Applicants assert that according to the teachings of Anil, et al, the effect of n-3 fatty acids on hepatic fatty acids is mediated through prostaglandins. However, the teachings of Anil, et al do not constitute factual evidence that n-3 fatty acids do not affect the level of expression of apoE. It is entirely plausible that n-3 fatty acids mediate an effect upon the level of expression of apoE by causing an effect upon the level of prostaglandin. For example, prostaglandins regulate the activity of transcription factors, e.g., PPAR- α , that in turn, regulate the expression of enzymes involved in β -oxidation of fatty acids and other catabolic pathways. These enzymes, in turn, regulate the level of lipoproteins and triglycerides in the serum. In fact, the hypolipidemic fibrates, such as gemfibrozil, which are administered to patients to combat hyperlipidemia, bind PPAR- α to regulate its activity. Contrary to Applicants' assertions, the teachings of Anil, et al do not serve to suggest that the agent of the prior art differs from the agent of the claims; rather the teachings of Anil, et al provide a possible nexus between the observations that dietary n-3 fatty acids cause a reduction in VLDL levels and apoE levels in the treated patient's serum.

Additionally, Applicants contend that on the basis of their results, i.e., those reported by Huang, et al, the dietary n-3 fatty acids of Connor, et al appear to have the opposite effect upon the level of LDL in the plasma should the dietary n-3 fatty acids act by decreasing the expression of apoE. Huang, et al found that over-expression of

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apoE3 in mice resulted in the accumulation of apoE3 in the serum of the transgenic mice and observed that the accumulation is associated with decreased levels of HDL in the serum and impaired VLDL lipolysis. However, Applicants have stated, "Huang et al. [...] teaches increased apoE results in normal or decreased LDL levels" (page 10, paragraph 3). Actually, Huang, et al teach that only after the transgenic mice over-expressing apoE3 were crossed to mice deficient in LDL receptor was a decrease in serum LDL observed (abstract). Nevertheless, regardless of the results of the studies reported by Huang, et al, Connor, et al teach that administering an effective amount of dietary n-3 fatty acids reduced VLDL, triglycerides, *and* apoE in the patients' plasma. Therefore, although Applicants may have predicted otherwise on the basis of their experimental results, administering dietary n-3 fatty acids appears to cause a decrease in VLDL by causing a decrease in the expression of apoE in the treated patients. Therefore, the agent of the prior art is deemed the same as the agent of the claims, absent a showing of any differences. Again, the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the product referred to in the claims. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed method or the products encompassed by the claims are functionally different than those taught by the prior art and to establish patentable differences.

New Grounds of Objection

14. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel claim 3, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Claim 3 recites the limitation "wherein said agent reduces the expression of apoE". However, claim 1 from which claim 3 depends, also requires the agent to reduce the expression of apoE. Accordingly, claim 3 does not further limit the subject matter of the claim from which it depends.

New Grounds of Rejection

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-8, and 11 are vague and indefinite because claims 1 and 5 recite the term "reducing" or "reduce". The terms "reducing" and "reduce" are relative terms. It is unclear to what extent the claims require the plasma level of VLDL to be reduced in practicing the claimed method. Furthermore, it is unclear to what extent the claims require the agent to reduce the amount of plasma active apoE in said host; and it is unclear to what extent the claims require the amount of expression of apoE to be reduced. Also, it is unclear to what amount of a reduction in the level of expression of apoE is regarded as sufficient to reduce VLDL production in said host, because it cannot be ascertained to what extent the level of VLDL production must be reduced. The specification provides no standard for ascertaining the requisite degree to which the levels of plasma active apoE, apoE expression, VLDL production, and plasma VLDL must be reduced. Accordingly, the artisan of ordinary skill would not be reasonably apprised of the metes and bounds of the claimed invention.

Claims 1, 4-8, and 11 are vague and indefinite because claims 1 and 5 recite the term "at least reduces". Recitation of the term renders the claims vague and indefinite because it cannot be ascertained what else the claims might require the agent to do in addition to reducing the amount of plasma active apoE. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claim 2 is indefinite because the claim recites the limitation "wherein said agent inhibits apoE". Recitation of the limitation renders the claim indefinite because it is unclear whether an agent that at least reduces the amount of plasma active apoE in

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said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production in said host by an amount effective to reduce the plasma level of VLDL in said host is also capable of inhibiting apoE. Moreover, it is unclear how the claim requires apoE to be inhibited. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claims 5-8 and 11 are indefinite because claim 5 recites "to treat said disease condition" in line 5. Recitation of the phrase renders the claim indefinite because it is unclear to what effect the disease condition is treated. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claims 5 and 11 are vague and indefinite because claim 5 recites the term "a disease condition associated with elevated plasma levels of VLDL". Recitation of the term renders the claim vague and indefinite because it cannot be ascertained how the disease condition is required by the claim to be associated with elevated plasma levels of VLDL. Furthermore, it is unclear whether Applicants regard their invention as a method for treating a host suffering from any disease in which elevated levels of plasma VLDL occur. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

17. Claims 1, 5, 6, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaskie, et al (*American Journal of Kidney Diseases* **15**: 8-15, 1990), as evidenced by Wyne, et al (*Journal of Biological Chemistry* **264**: 16530-16536, 1989).

Kaskie, et al teach a method for treating patients diagnosed with a hyperlipidemia. The method of Kaskie, et al involved administering to a patient an effective amount of lovastatin, an inhibitor of hydroxymethylglutaryl (HMG)-CoA reductase, to reduce the production of VLDL in the patient to reduce the level of VLDL in the plasma of the patient.

As evidenced by the teachings of Wyne, et al, mevinolin, i.e., lovastatin, attenuates the production of mRNA encoding apoE in cells, thereby suggesting that the

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agent acts by a mechanism that involves reducing the expression of apoE. Therefore, the agent of the prior art and the agent of the claims are deemed the same, absent a showing of any differences. The Office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the product referred to in the claims. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed method or the products encompassed by the claims are functionally different than those taught by the prior art and to establish patentable differences.

Conclusion

18. No claims are allowed.

19. The art made of record and not relied upon is considered pertinent to Applicants' disclosure. Lafitte, et al teach a mechanism by which the expression of apoE is regulated. Ogbonna, et al teach that the expression of apoE is regulated by insulin at the translational and post-translational levels. Garg, et al teach that insulin is administered to patients diagnosed with diabetes; furthermore, Garg, et al teach that dyslipidemia is secondary to diabetes. Colwell, et al teach that aspirin is administered to patients diagnosed with diabetes and hyperlipidemia. Petegneif, et al teach that aspirin is an inhibitor of the transcription factor NF- κ B and that NF- κ B regulates the expression of apoE. Krul, et al teach that insulin causes a reduction in the amount of apoE secretion by astrocytoma cells. Civeira, et al, Lane, et al, and Pauciullo, et al teach that gemfibrozil therapy causes a reduction in the level of expression of apoE as evidenced by a reduction in the level of apoE in the plasma of patients treated with gemfibrozil. Dvorchik, et al teach limitations of antisense therapies. Bremer, Neve, et al, and Pineda Torra, et al teach the role of PPAR in atherosclerosis.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

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(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.

Examiner

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slr

July 27, 2001

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